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Disease-a-Month

The Nephrotic Syndrome

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THE NEPHROTIC SYNDROME is a disease entity characterized by edema, proteinuria, low serum albumin and protein concentration, and hyperlipemia. It appears most frequently in young children but may occur at any age (Fig. 1). The course usually extends over many months or years. Fluctuations in edema are seen, especially after intercurrent infection. In no more than half of a large group of patients, spontaneous evolution of the disorder leads to healing. The remaining patients succumb to infection and other intercurrent hazards or, ultimately, to hypertension and uremia. Although new and effective methods of treatment have been developed, the disease presents a real challenge to the physician.

In most cases, the etiology is uncertain. The course and findings vary from case to case. Pathologic classification is usually

made in retrospect and is therefore not helpful in establishing prognosis or in determining treatment during life. Nomenclature is not definitive or generally agreed upon. Serial study of the patient and repeated biopsy have indicated that progressive alterations in physiologic and anatomic pathology may occur. It seems proper, therefore, to define typical patterns of the disease before discussing current views of pathogenesis and differential diagnosis.

CONSTITUTIONAL AND PRECIPITATING FACTORS.—Rarely the disease may appear in the neonatal period. Most cases appear

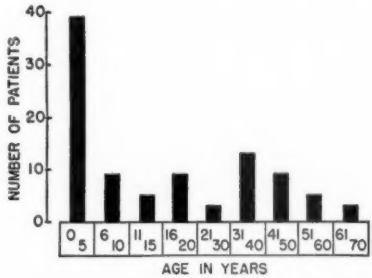

FIG. 1.—Age at onset of nephrotic syndrome (93 patients observed at Stanford University Hospitals from 1949 to 1955).

between the second and fifth years of life. There is a somewhat higher incidence in males. Fanconi and his co-workers (1) observed a nephrotic syndrome in several children of the same family. In approximately half the cases there is an allergic diathesis in the family and in the patient. This observation takes on added significance when the nephrotic syndrome follows known allergic episodes, precipitated by exposure to pollen, poison oak, or bee sting (2). In other cases, hypersensitivity to drugs has been suspected or proved.

In about one third of the cases, respiratory infection precedes the onset, but this is by no means so regular as in acute glomerulonephritis. Prior infection with hemolytic streptococcus is very seldom demonstrable in the nephrotic syndrome, even when the patient is seen soon after appearance of symptoms or signs.

CLINICAL COURSE.—In many instances, insidious, increasing edema is the first recognized evidence of disease. Lassitude, weakness, faintness, or syncope may be noted. Gain in weight precedes visible edema. Swelling is usually noted first about the eyes and face or in the ankles, gradually extending to thighs, back, abdomen, and genitalia. Effusions into abdomen and pleural spaces lead to dyspnea and orthopnea. Atelectasis with basilar râles may be noted, but signs of pulmonary edema are seldom found. Blood pressure is usually normal.

As edema increases, loss of appetite, nausea, diarrhea, and irritability are common. Progressive malnutrition usually develops, especially in those patients who remain untreated for long periods. Since calcium balance is affected, together with the obvious disturbances of general nutrition and protein metabolism, children with the nephrotic syndrome show temporary slowing of growth.

Increased susceptibility to infection is regularly seen in children, especially as debility progresses. Cellulitis, peritonitis, and invasion of the blood stream are common. Fever, irritability, and loss of appetite should initiate a search for local or generalized infection. Prompt treatment of such crises with broad-spectrum antibiotics usually results in amelioration of the condition. If timely and effective treatment is not given, intercurrent infection may be fatal.

Infection often aggravates the edema and proteinuria. Severe or generalized infection is occasionally followed by diuresis and clinical improvement. All manifestations of disease may disappear; but, more often, the continuation of proteinuria indicates that the renal lesion is still active. Improvement may be temporary, or complete and permanent. It has been suggested that prevention or interruption of infection by the use of antibiotics may have diminished the chance of remission and thus modified the course of the disease adversely. However, since infection in these patients is dangerous, frequent, debilitating, and offers no guarantee of an effective or permanent remission, it is not surprising that survival rate has improved since antibiotics have become available.

In many cases, remission does not occur. The patient becomes bloated, wasted, and confined to bed. In addition to the gen-

eral discomfort, massive edema leads to respiratory distress and gastrointestinal symptoms. Distention of the abdomen may lead to diastasis recti, umbilical hernia, and rectal prolapse. Breaks and infection of the skin are common. A substantial quantity of fluid may leak through a break in the skin or through the opening left following paracentesis.

The psychologic hazards of this disease are also serious, both for the patient and his family. Gradual, progressive debility prevents the patient from carrying on a normal life. He becomes

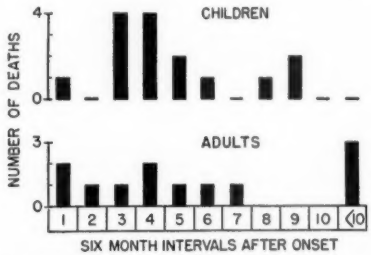

FIG. 2.—Number of deaths in each six-month interval after onset of nephrotic syndrome. Between 1949 and 1955, there were 15 deaths among 44 children and 12 deaths among 42 adults.

increasingly anxious to achieve some improvement as months pass. If none occurs, he is likely to shop around for help and to do some reading in the medical literature, with disheartening results. Reassurance of the patient and his family is very important. Potential survival and recovery must be emphasized. The physician's aim is not only to relieve symptoms and manifestations, such as edema, but also to take all measures to promote healing of the renal lesion. This stand has been easier to take in recent years since treatment has allowed the physician to eliminate edema by methods which do not impair renal function but rather offer some hope of improving function.

LONG-TERM COURSE AND OUTCOME.—The duration of the nephrotic syndrome is measured in months or years. In children, the renal lesion usually leads to healing or renal insufficiency within three years. In adults, the disease may continue to evolve

over five years or longer (Fig. 2). If the disease is allowed to persist untreated for long periods, there are serious risks. More than one third of a group of children followed over a period of years died of intercurrent complications (3). Infection, sudden heart failure, edema of the lungs and brain, and extensive thromboses involving the aorta or pulmonary artery were observed. In adults observed at Stanford, venous thrombosis is common, arterial occlusion rare. These intravascular clots are usually localized and benign but occasionally cause death from pulmonary embolism or thrombosis of a major vessel.

Previous studies have shown that the outcome in children is more favorable than in adults. It is an exaggeration, however, to state that the outcome is uniformly favorable in children and hopeless in adults. Nephrosis is highly fatal in the neonatal period. Before the use of corticosteroids was introduced, there was no better than a 50% recovery rate in children with the nephrotic syndrome. Some adults show a remittent and benign course which ultimately goes on to healing, even without specific therapy. Addis (4) found 11 adult patients with this form of disease, representing a substantial proportion of his adult cases of the nephrotic syndrome.

In some adults, especially in men, edema is less marked, while signs of a destructive renal lesion are more prominent. This syndrome blends imperceptibly with the form of chronic glomerulonephritis described by Ellis as "Type 2."

It remains to be seen whether these differences are due to variations in incidence of different diseases in different age and sex groups or whether we are dealing with the same disease which takes different forms depending on the constitution or hormonal status of the individual case.

A cyclical form of nephrosis has been described by Addis (4). These subjects may show repeated episodes of typical nephrotic pattern with intervals of normal urine, serum protein, and cholesterol. Such patients may then go on to heal or may continue to have recurrences, ending in renal insufficiency.

Detailed study of the renal function demonstrates reduction of renal excretory function early in the course of most patients with the nephrotic syndrome (5). An occasional case shows temporary increase in renal function in the first few months

after onset of the disease. Glomerular filtration rate is reduced out of proportion to reduction of the renal plasma flow (i.e., low filtration fraction). These reductions are not usually sufficient to have clinical consequences. The serum creatinine is usually within normal limits, although serum urea concentration may be increased. Although these tests do not furnish an infallible prognostic index, they measure the remaining reserve of renal function. If serial tests are done, the direction and speed of change may also be indicated.

As time passes, some patients with the nephrotic syndrome show regular and increasing hematuria and hypertension. In many of these cases, renal function deteriorates steadily until serum creatinine and urea rise above normal and acidosis becomes marked. Within a few years after onset, between one third and one half of children with this disease die in renal insufficiency. In adults, the prognosis is even less hopeful, but the evolution of the disease is slower.

Although it is frequently stated that many patients lose their edema before death in uremia, only two of Rennie's 29 patients died without edema (6). The progressive decline of renal function is usually slow and inexorable, but sometimes acute exacerbations occur during which renal function is grossly diminished. Hypertension usually appears and increases as renal function diminishes. In certain instances, hypertension of a severe grade may occur while renal function is still reasonably good. Symptoms and deleterious effects on vision and cardiac function indicate specific therapy if renal function is adequate. The common terminal hypertension of uremia, on the other hand, seldom justifies more than symptomatic measures.

CLINICAL-PATHOLOGIC CORRELATIONS AND REFLECTIONS ON TERMINOLOGY

Because of the limitations of his diagnostic methods, the clinician leans heavily on the pathologist for a "final diagnosis." In the past, a diagnosis of glomerulonephritis depended on the presence of specific lesions visible in stained sections of kidney tissue. If no such changes were seen, there was no basis for this pathologic diagnosis, even though the patient might have shown

clear evidences of functional glomerular pathology, as well as a clinical course and laboratory findings indistinguishable from the patient with obvious glomerular lesions. This fundamental difference in viewpoint of clinician and pathologist has led to confusion in nomenclature and thought.

PATHOLOGIC TERMS.—In its simplest meaning, "glomerulonephritis" denotes inflammation of glomeruli and its consequences; it does not imply a single etiology or course for its various forms. "Nephrosis" is used by some observers to describe degenerative changes in the kidneys, including a great variety of disease and intoxication (e.g., "mercurial nephrosis" or "lower nephron nephrosis"). The accumulation of hyaline and fatty droplets in tubular epithelium in the nephrotic syndrome is now thought to be secondary to increased glomerular permeability to protein; the term "lipoid nephrosis" has been applied to such cases when glomerular lesions were not demonstrated by conventional technics. Classifications based on these nonspecific descriptions are inadequate for clinical use.

More recently, Bell (7) has demonstrated systematic differences between two forms of glomerulonephritis, corresponding with differences in clinical findings and course. "Diffuse proliferative glomerulonephritis" is observed in acute, poststreptococcal, hemorrhagic nephritis and its sequelae. The most prominent features are endothelial proliferation, occluding capillaries, and epithelial proliferation, forming crescents and compressing glomeruli. "Membranous glomerulonephritis" corresponds with what the clinician calls "lipoid nephrosis" or "nephrotic syndrome" or "degenerative stage of chronic glomerulonephritis." This disease differs from proliferative glomerulonephritis in that the chief disturbance is due to permeability to proteins rather than to capillary obstruction. In young children and in cases of short duration the glomerular lesion may not be visible by conventional technics, although alterations of basement membrane and "podocytes" (epithelium) are seen on electron microscopy. In long-standing cases and in adults, thickening of basement membrane becomes more pronounced, narrowing the capillaries to complete occlusion, with hyalinization of glomeruli and progressive loss of renal function. There are marked similarities between these lesions and those observed in some patients

with disseminated lupus erythematosus or toxemia of pregnancy. Allen (8) also emphasizes glomerular lobulation into hyalinized spheres, which resemble in some ways the alterations seen in diabetic glomerulosclerosis, lupus erythematosus, and amyloidosis.

CLINICAL-PATHOLOGIC CORRELATIONS.—Longcope (9) noted that most patients with acute, poststreptococcal nephritis survive and go on to healing. On the other hand, most patients who die of "chronic glomerulonephritis" give no history of an acute attack but have an insidious onset of proteinuria, with or without edema. Ellis (10) described differences in pathologic findings in these two groups, which he designated as Type 1 (acute, benign) and Type 2 (chronic, insidious, fatal). In the nephrotic syndrome, Ellis found no visible pathologic changes in cases of brief duration. Active cases of long standing showed changes similar to those of Type 2 nephritis.

Ehrich, Forman, and Seifter (11) have also emphasized that the histopathology of the nephrotic syndrome is quite different from that of acute, diffuse glomerular nephritis. When the nephrotic syndrome was of short duration and not accompanied by renal insufficiency, the glomeruli showed thickening and splitting of basement membrane, while hyaline masses, focal scars, and rare adhesions were noted in a few cases. In cases of longer duration, in which hematuria, hypertension, and renal insufficiency had developed during life, the kidneys showed advanced changes in basement membrane, obliteration of capillaries, and hyalinization of glomeruli. Endothelial and epithelial proliferation was not consistent or prominent. Around some obliterated glomeruli there were thick crescent-like structures which stained blue in Ritter-Oleson acid-periodate-polysaccharide stain, as if related to hyaluronic acid.

Bjornboe *et al.* (12) demonstrated similar changes by biopsy of the kidneys. They classified their cases as "lipoid nephrosis," transition form, or chronic glomerulonephritis (Ellis Type 2), according to the severity of glomerular changes, which consisted of "prehyalinization" of basement membranes in all cases.

All these observers noted hyaline droplets and fat in epithelium of proximal tubules. These are generally considered to be secondary to the glomerular lesion.

CLINICAL OBSERVATION AND LABORATORY TESTS.—In the

early stages of the nephrotic syndrome, physiologic studies have demonstrated increased permeability of glomeruli to proteins, especially smaller molecules such as albumin and α-1-globulins, even when available stains and light microscopy show no visible alterations in glomerular structure. "Pure lipoid nephrosis" and the nephrotic syndrome terminating in "chronic glomerular nephritis" are indistinguishable at the onset. Differentiation is possible only in retrospect after long follow-up and autopsy.

THE UNITARIAN CONCEPT.—Clinicians (5, 13, 14) have thus been led to the viewpoint that they are dealing in most cases with a single disease, which may either become inactive with little or no residual impairment of renal function or, in other cases, may progress to irreversible glomerular alterations and renal insufficiency. This viewpoint is supported by the clinical and pathologic observations already described, which offer no evidence that two separate disease processes are at work. In this review, no effort will be made to differentiate between early stages and nondestructive forms of the nephrotic syndrome ("lipoid nephrosis") and those going on to renal insufficiency. The term "membranous glomerulonephritis" will be used, as suggested by Bell. It is recognized that other diseases sometimes produce similar morphologic changes. At the moment, however, a more apt descriptive term has not been suggested. Other names, such as "lipoid nephrosis," have developed such fixed connotations that further confusion is inevitable if an old term is used in a new sense. When the etiology of the disease is known, a definitive name may qualify or replace the present descriptions.

PATHOGENESIS

1. MEMBRANOUS GLOMERULONEPHRITIS.—The etiology is unknown. Similar glomerular lesions and physiologic changes can be produced in rats by the injection of nephrotoxic serum (11, 15). If it can be inferred that some immunologic mechanism is responsible for the human disease, it may be of interest that half the patients give a family or personal history of allergic disease. Various overt allergic reactions may initiate or aggravate the nephrotic syndrome. Severe hay fever, heavy exposure to poison

oak, and bee stings have precipitated the nephrotic syndrome in sensitive individuals (2). The syndrome has also followed the use of certain drugs, including tridione® and related compounds, gold, calomel, and bismuth (1, 14). In some cases, withdrawal of the offending agent may be followed by improvement.

2. Acute, diffuse glomerulonephritis.—A typical attack of acute hemorrhagic nephritis rarely ushers in a nephrotic syndrome. Cases have been described in which the nephrotic syndrome has followed immediately after an acute attack and has progressed within a few months to renal insufficiency. In other instances, some features of the nephrotic syndrome appear during the course of chronic glomerulonephritis. Cases in which the initial attack can be interpreted unequivocally as acute hemorrhagic nephritis are exceptional.

A different view is presented by Loeb (16) in his classic description of glomerulonephritis, of which the nephrotic syndrome is considered to be a phase. Possible differences in interpretation are illustrated by two charts (Figs. 135 and 137, Ref. 16). In one patient, disease "began with classical acute glomerulonephritis" following a sore throat; but the signs illustrated are those of the nephrotic syndrome—edema, proteinuria, hypoproteinemia, very high serum cholesterol. The blood pressure was normal; hematuria was absent, and renal function was normal. Over the course of three years, this patient developed increasing hematuria, anemia, hypertension, retinitis, and fatal renal insufficiency. In the second patient, the disease was first recognized with the appearance of the nephrotic phase. Both these patients showed undoubted evidences of "chronic glomerulonephritis" during the course of their disease. They are examples of the nephrotic syndrome in adults, regardless of differences in interpretation as to etiology.

There are diseases which produce a clinical pattern so like the common type of nephrotic syndrome that differentiation may be impossible for a time, and the diagnosis may become apparent only on pathologic examination. These include bilateral obstruction of renal veins, amyloidosis, and disseminated lupus erythematosus.

3. Bilateral obstruction of renal veins.—Thrombosis of both renal veins, frequently associated with thrombosis of inferior vena cava and sometimes with involvement of hepatic

veins, may lead to intense proteinuria with a nephrotic syndrome. This is not the only syndrome associated with renal vein thrombosis; infarction and acute renal insufficiency may occur. It may not be apparent even after postmortem examination whether the thrombosis is the cause or a result of the nephrotic syndrome. Extensive venous thromboses in other areas are commonly seen during the nephrotic syndrome. The absence of visible glomerular lesions in these patients is not conclusive evidence in the question of etiology. It is easy to visualize that such extensive venous obstruction might give rise to intense proteinuria and a nephrotic syndrome. A similar picture may occur in constrictive pericarditis and may be relieved by surgical correction of the obstruction (17).

The diagnosis may become evident if increased venous pressure or collateral circulation is noted. Paracentesis and repeated observations are necessary to rule out pressure on the vena cava by tense ascites. The situation is seldom recognized during life.

4. Amyloidosis.—In patients with chronic suppurative diseases, tuberculosis, syphilis, or rheumatoid arthritis, probability favors amyloidosis as the basis of a nephrotic syndrome. In some instances, only proteinuria appears, or hyperlipemia and hypertension may be absent or renal insufficiency occurs early; but in other cases, a typical nephrotic pattern is seen. There may be evidences of involvement of other organs: a large, firm liver should arouse suspicion. Gamma globulin content of serum may be high as contrasted with the low levels often seen in the nephrotic syndrome (18). Biopsy of liver or kidney will usually give a definitive answer (12). Early excision of a suppurative focus offers the only hope of stopping the progress of the disease. The response to steroids is usually incomplete, although some diuresis may occur after treatment.

5. Disseminated lupus erythematosus.—In this disease, the renal lesion is variable, but pathologic changes in the glomeruli, heavy proteinuria, and a nephrotic syndrome are occasionally seen. In the early stages, when only the renal disease is evident, the true diagnosis may not be obvious. Fever, arthralgia, cardiac murmur, skin rash, and other manifestations of disseminated disease usually call attention to involvement of other organs. The renal lesion of disseminated lupus erythematosus responds poorly to steroid therapy. Diuresis and modest im-

provement of function may appear, but most cases follow a chronic and progressive downhill course (19).

6. Toxemia of pregnancy.—Proteinuria, hypoproteinemia, and edema, with or without evidences of hypertensive cardiovascular disease, occurring during the last trimester of pregnancy are most often due to "toxemia" of pregnancy. The nephrotic syndrome may pre-exist and become obvious during pregnancy, but signs usually develop earlier than those associated with toxemia. Final differentiation may not be possible until after delivery.

There are diseases in which a syndrome somewhat resembling the nephrotic pattern may appear but in which evidences of the underlying disease are usually obvious.

7. Intercapillary glomerulosclerosis.—Patients with long-standing diabetes mellitus may develop proteinuria, hypoproteinemia, edema, and high serum cholesterol. The history of diabetes mellitus, the presence of glycosuria or of hyperglycemia with high renal threshold, the typical retinopathy of diabetes, and prominent hypertension with early cardiac failure even before renal insufficiency becomes marked, are unusual in ordinary forms of the nephrotic syndrome. Differential diagnosis should present no problems except in the last stages. Conservative treatment is unsatisfactory.

8. Secondary syphilis.—The nephrotic pattern may also occur during the course of secondary syphilis. Since there are usually other signs (fever, rash, adenopathy), the differential diagnosis should not be difficult. A serologic test for syphilis should be performed routinely in patients with the nephrotic syndrome. The abnormalities of the plasma proteins in nephrosis may interfere with the serologic test, but positive reactions are not common in patients with the ordinary form of nephrosis. A false positive test for syphilis is found occasionally in disseminated lupus erythematosus. With these factors in mind, a careful history and physical examination should lead to the correct diagnosis.

LABORATORY FINDINGS

The most typical and characteristic manifestation of the nephrotic syndrome is heavy proteinuria. As much as 20 Gm. per day may be excreted in some individuals, but the usual daily

protein loss is between 3 and 10 Gm. per 24 hours. Between 50 and 90% of the urine protein is albumin, even when the serum albumin has been reduced to extremely low levels. The urine is usually concentrated and acid. Reducing substances may be found in small quantities. During the collection of edema, the output of sodium and chloride is very low.

The *urine sediment* may be negligible in the earliest stages. Later, hyaline and granular casts appear. Renal epithelial cells are seen as intact cells or in various stages of degeneration and disintegration into fatty droplets, often caught in casts. Oval fat bodies appear; these typical, large, round epithelial cells, swollen with refractile droplets of fatty material, are characteristic of the nephrotic syndrome. Red blood cells are variable in number from case to case, and from time to time in the same individual. Blood casts are rarely seen. In a typical case of short duration, quantitative examination (Addis) shows 0 to 5 million erythrocytes per 24 hours. However, some children and many adults excrete from 10 million to 100 million red cells per day.

Examination of the blood often shows a high hematocrit early in the disease, as might be expected with loss of protein and plasma volume. Later this falls to normal or below. A moderate normocytic anemia is characteristic of the middle stages of the disease. The absolute number of eosinophils circulating in the blood is increased, sometimes quite strikingly. The sedimentation rate is very rapid.

Plasma or *serum* is creamy. All lipids are increased, especially neutral fat, which coalesces into visible droplets, particularly when blood is drawn after a meal. Chemical examination of blood shows a reduced total serum protein concentration, usually between 2 and 4.5%. Albumin may be moderately reduced or almost absent. Total globulins tend to be normal in concentration.

When serum or plasma is examined by *electrophoresis,* the pattern is quite typical. There is very marked reduction in albumin and gamma globulin. Alpha-2 and beta-lipoproteins are greatly increased, and fibrinogen is present in large amounts. When examined in the ultracentrifuge, all fractions of lipoprotein aggregates are increased. All fractions of the blood lipids are increased. Neutral fat may be especially high. Both the free and

esterified forms of cholesterol are increased in concentration.

OTHER CHEMICAL TESTS.—Blood urea concentration tends to be high, even in the early stages of this disease, perhaps as a consequence of oliguria. Creatinine concentration in serum, on the other hand, is usually normal. There is usually some reduction in serum sodium concentration and in serum bicarbonate. Serum chloride is usually increased. The hyponatremia observed in the nephrotic syndrome is to some extent an artefact related to the high concentration of lipids in the blood and the corresponding reduction in serum water content. Renal clearance of endogenous or exogenous test materials (urea, creatinine, inulin, para-aminohippurate) may be high in the initial stages of the nephrotic syndrome, but within a few months the clearances are subnormal and tend to remain low or to decrease further as the disease progresses.

The *antistreptolysin-O titer* is almost invariably low (i.e., 12 units or less) in the nephrotic syndrome, in contrast to the high levels which typically accompany an acute attack or exacerbation of poststreptococcal glomerulonephritis (9). The low level does not appear to be related to loss of antibody in urine (20). *"Complement"* is depressed in serum of patients with nephrosis (48).

SIGNS OF RENAL FAILURE.—Loss of concentrating power is an early sign. Reduction in albumin in urine and increase in the proportion of globulin in urine protein may occur. Broad casts appear. Red blood cells are found more regularly and in larger numbers in many cases. Anemia becomes more prominent. Acidosis and other disturbances of electrolyte concentration are common. Serum creatinine and urea levels rise as renal clearances fall. Repeated estimation of renal function may show a steady decline long before signs of renal failure become apparent; but some children, who maintain low levels of renal function over long periods, regain workable or nearly normal function following healing of the disease.

PHYSIOLOGIC PATHOLOGY OF THE NEPHROTIC SYNDROME

Proteinuria is, by definition, an essential part of the nephrotic syndrome. One of the several known or unknown etiologic agents,

acting in sensitive individuals, initiates a glomerular lesion characterized by alteration of the filtering membrane. When the "pore size" of the membrane is increased, some smaller protein molecules pass through the glomerular membrane, and proteinuria ensues. Some protein is "reabsorbed" by tubular epithelium, but failure of such absorption is probably not the major factor in proteinuria (21, 22, 23).

Long-continued, heavy proteinuria with a high clearance of albumin must have a depressing effect on the circulating levels of plasma albumin. There is some doubt, however, as to whether the loss is adequate to explain the marked reduction in circulating albumin which exists in the nephrotic syndrome. Other patients with equally heavy proteinuria do not show corresponding depletion of circulating albumin. Normal men, like normal dogs, tolerate loss of large amounts of plasma protein for long periods without depression of the plasma proteins, so long as an adequate protein intake is maintained (24). Statistical correlation of hypoproteinemia and proteinuria is meaningless in a disease in which both these manifestations must be present by definition and from which we exclude patients with only one of these signs. Patients with idiopathic hypoproteinemia, for example, have plasma albumin deficiency comparable to that of the nephrotic syndrome without proteinuria. In these patients, as well as in the nephrotic syndrome, an increased rate of metabolism of circulating albumin has been demonstrated, using radioactive tracer technics. This may be related to the greatly depleted level of albumin in the circulating and extravascular "pools." Perhaps for this reason, reduction or disappearance of proteinuria in the nephrotic syndrome is not regularly followed by prompt return of the circulating proteins to normal.

Thus, there are at least three factors which tend to depress plasma protein concentration—loss of protein in urine, increased metabolism of circulating albumin, and general protein depletion, in part due to malnutrition.

A fourth factor in hypoproteinemia is dilution. When concentrated human serum albumin is injected intravenously (25 Gm. twice a day for four days), a sharp rise in plasma volume ensues (25). In about half the patients so treated, diuresis ensues, and plasma protein concentration increases. If the excretion of sodium

and water is not increased, however, the albumin added to plasma is diluted by edema fluid, and plasma protein concentration is not increased. This failure is not due to total loss of injected albumin in urine, as has been sometimes claimed. Substantial amounts of protein are retained in the body, and total circulating protein can be raised acutely to nearly normal levels. For every gram of protein added to plasma, 25 ml. or more of interstitial fluid is drawn into the plasma by osmotic forces.

Protein added to the circulation is diluted, but it mobilizes edema fluid, increases plasma volume and intravascular pressures, and improves circulation and filtration in the kidneys. The degree of improvement of renal function roughly measures that part of the functional impairment which depends on circulatory inadequacy and renal vasoconstriction. Improved diuresis and sodium excretion may follow somewhat later after plasma volume and renal function have been increased and maintained for a time.

Epstein's interpretation of nephrosis, in terms of loss of protein = hypoproteinemia = reduced colloid osmotic pressure = edema, was a milestone in the advance of physiologic understanding; but this explanation does not take into account renal handling of sodium and water as the critical factor in accumulation or relief of edema. Addis expressed the dissatisfaction felt by many: "No clinician is so naïve as to regard the relation between edema and plasma protein concentration as an adequate explanation . . ." (4).

Variations in sodium excretion are not satisfactorily explained by alterations in renal blood flow and filtration, which affect sodium excretion in acute experiments but have little effect on day-to-day sodium balance in man. In the nephrotic syndrome, edema may be present when renal plasma flow and glomerular filtration are normal or supranormal as well as in cases with reduced renal function (26). These findings suggest that sodium and water balances of man are controlled by mechanisms acting on the renal tubules. Increased levels of antidiuretic substances have been observed in nephrosis (27).

Recently, the potent, sodium-retaining, adrenal cortical hormone, aldosterone, has been found in unusually large amounts in urine of edematous patients (28). Administration of this hormone in more than physiologic dosage for several days leads to

reduced sodium excretion and edema in patients with rheumatoid arthritis and other conditions not ordinarily associated with edema (29). It seems likely that an excess of endogenous aldosterone is present in the edematous patient with nephrosis, since the quantity of active hormone found in the urine is usually at least ten times that obtained from urine of normal men. When administration of cortisone or intravenous albumin is followed by relief of edema, the output of aldosterone diminishes as diuresis increases (30). When treatment fails to reduce aldosterone output, sodium excretion does not increase. Other patients with congestive heart failure, hepatic cirrhosis, and toxemia of pregnancy also show increased output of aldosterone during periods of edema and impaired sodium excretion. Thus in all of these patients and in normal men, there is a strong inverse correlation between aldosterone output and sodium excretion (31).

Stimuli known to increase aldosterone output in normal men are sodium depletion, dehydration, and potassium loading. Corticotropin administration causes only a brief and small increase in aldosterone, followed by a decrease below control output (31). Why is the presence of an excess of water and sodium associated with increased aldosterone output in the nephrotic state, while much smaller degrees of overhydration abolish aldosterone output in normal men?

A clue may be found in the observation that infusion of albumin increases plasma volume and decreases aldosterone output in nephrosis. Acute reduction in circulating protein results in decreased plasma volume. Reduction in cardiac output and in blood flow through viscera follows when more than a small fraction of plasma volume is lost. This process seldom reaches the point of total circulatory collapse, although postural hypotension and syncope may be seen in the early stages of the nephrotic syndrome.

"Circulatory inadequacy" has been postulated by Borst (32) and Peters (33) as the common factor in several diseases associated with edema due to diminished renal excretion of sodium. These are the same circumstances in which aldosterone output is increased. It is thought that retention of sodium and water may represent an effort to compensate for the reduced plasma volume. Edema might thus be considered a by-product of the body's effort

to sustain and improve the circulation of blood. This hypothesis will require further experimental support, but, for the moment, it provides a reasonable explanation for observed phenomena.

The high level of blood lipids is also thought to be a consequence of depletion of serum albumin (34). Hypercholesterolemia appears to be due to a "traffic jam," as Addis suggested, related to deficiency of circulating albumin and difficulty in metabolizing large beta-lipoprotein complexes.

These aspects of the nephrotic syndrome are essentially reversible. After glomerular perfusion and permeability return to normal, all of the consequences gradually disappear. This phenomenon is seen during treatment with corticotropin or cortisone, after infection, and occasionally without obvious cause. Under similar circumstances, diuresis may also occur without appreciable improvement in renal function or reduction in proteinuria. It is obvious that, in the nephrotic syndrome, aldosterone production and other factors controlling excretion of sodium and water are subject to opposing influences. In the course of the disease, sodium and water retention is initiated, but progressive accumulation of extracellular fluid sets in motion the homeostatic machinery which should suppress or override the sodium-retaining mechanisms. It is not surprising that in some instances diuresis may wax and wane without significant change in proteinuria.

Irreversible changes in glomeruli may occur during the course of the nephrotic syndrome. Thickening of basement membrane may progress to focal or complete hyalinization of glomeruli, with obliteration of capillaries and capsular spaces. This gradual loss of functioning nephrons is reflected by the secretion of urine of fixed, low specific gravity and by progressive chemical alterations in the blood as renal excretory and regulatory functions fail (5). Ultimately, hypertension and uremia appear. These phenomena are not dependent on the physiologic disturbances which were present early in the disease. In some cases, proteinuria and edema become less prominent as destruction of glomeruli leads to renal insufficiency.

Two separate factors stand out in the mind of the physician as he looks back over the course of the disease: (1) the protein

depletion and edema, with all its discomfort and debilitating effect on the patient, and (2) the destructive capacity of the renal lesion, which determines the ultimate outcome.

MANAGEMENT OF THE NEPHROTIC SYNDROME

Advice and therapy should be directed primarily toward the survival and ultimate recovery of the patient. Survival depends on the avoidance of intercurrent hazards, notably, infection, malnutrition, and massive edema as well as hypertension, cardiac failure, and acute exacerbations of the renal disease. But in the long run the outcome depends on cessation of activity of the renal lesion. Clinical relief may occur without fundamental alteration in the renal lesion or of its consequences. Such temporary relief is much sought for by patients and their families but should not deceive the physician as regards the necessity for further treatment and improvement in the underlying disease. All therapy, both symptomatic and fundamental, should be evaluated not only for effectiveness but also for possible risks, immediate and long range.

There is no indication for prolonged bed rest or hospitalization in the majority of cases. It may be desirable to hospitalize the patient for initial study or treatment of specific problems. Edema may be reduced in some patients by periods of bed rest which enhance diuresis. In other patients, no weight loss occurs at bed rest, while the redistribution of fluid upward from legs into genitalia, abdomen, and pleural spaces may only aggravate the patient's discomfort and cause increasing respiratory distress. Common sense should dictate the amount of activity and rest in any patient. There is no evidence that prolonged periods of bed rest affect the long-term course of the disease. Variations in proteinuria related to posture or exercise may be discounted.

Fluid intake should be generous. Undesirable retention of urea, potassium, and other substances in blood and body fluids follows marked reduction of water intake. Restriction of water intake may be necessary for brief periods when stress or exacerbation leads to oliguria, symptoms or signs of water intoxication, and hyponatremia.

A diet of low-sodium content is recommended during periods

of edema, when the patient's sodium excretion is impaired. Low-sodium diets are satisfactory in controlling fluid accumulation in certain patients, if sodium restriction is followed by constant or falling weight. But if fluid continues to accumulate on a very low sodium intake, hyponatremia is likely to ensue. During periods of marked water retention, especially during the early days of adrenal steroid therapy or following paracentesis, a diet containing at least 2 or 3 Gm. of sodium chloride is advisable.

High potassium intake is sometimes indicated, especially after prolonged dietary inadequacy, nausea, or diarrhea, and during long-term use of cation exchange resins or adrenal steroids. Some patients, however, are unable to excrete additional potassium during periods of oliguria or impaired renal function or in the presence of marked sodium depletion; under these circumstances, a high potassium intake may be dangerous.

There is no general agreement on the proper protein intake. Epstein's early observations on the nephrotic syndrome indicated the marked protein depletion, and it was thought that a high protein intake was desirable (35). Indeed, in certain patients with marked malnutrition, a prompt beneficial effect is evident. In most patients, however, little effect on the edema or plasma protein concentration is apparent. Diets very high in protein are unpalatable; children frequently reject them.

Addis (4) advocated a low-protein diet to diminish the work of the kidney by reducing the quantity of metabolites and other materials to be excreted. If protein intake is greatly reduced, additional calories must be given in the form of carbohydrate and fat, and supplementary vitamins and minerals are needed. There is strong experimental evidence that a low-protein diet can improve the well-being and survival of animals whose effectively functioning renal tissue has been severely reduced by disease or surgery. Very low protein intake is recognized as essential in acute renal insufficiency and may be advantageous in some cases of chronic renal insufficiency, but there is as yet no evidence of beneficial effects of prolonged low protein intake in the nephrotic syndrome.

In many chronically ill patients, and especially in children, any dietary restriction results in a diminution of food intake. Severe nutritional deficiency may follow the child's refusal to eat an

unusual diet. Anorexia and poor food intake usually result in a low-sodium, low-protein diet in any case. The most important indication is to maintain a reasonable state of nutrition. Simple foods of high carbohydrate and caloric value are helpful in this respect.

Infection is a major hazard, especially to children with the nephrotic syndrome. Patients should be advised to avoid exhausting exertion, severe chilling, and other factors which might diminish resistance. In susceptible children, contacts should be reduced without resorting to complete isolation. We have generally not admitted our patients to the hospital except for special study or treatment, since hospitalization is frequently associated with intercurrent infection. This attitude has been fortified by the recent development of antibiotic-resistant strains of bacteria in many hospitals. The increased incidence of active infection with resistant organisms has also discouraged the prophylactic use of antibiotics. On the other hand, intercurrent infection should be treated promptly and fully with a specific antibiotic or with a "broad-spectrum" agent or combination if the organism is not identified. In communities or institutions where there is a high incidence of bacterial infection during winter and spring, or in highly susceptible children, prophylactic antibiotic administration may be desirable; but the physician must be on guard against infection with resistant gram-negative bacteria or staphylococci.

Infection poses a tantalizing paradox. It may precipitate recurrence of the nephrotic syndrome in a patient who is temporarily in remission, but it may also induce improvement or remission of the nephrotic syndrome. It has been suggested that reduction in frequency or severity of infection may diminish the number of natural remissions, but effective use of antibiotics has reduced morbidity and immediate fatality rate.

Deliberate induction of measles, dengue fever, and malaria has resulted in improvement of patients suffering from the nephrotic syndrome (36, 37, 38). Intercurrent infection with hepatitis has also had a similar result. Inoculation with vaccinia, yellow fever vaccine, or influenza vaccine may be followed by improvement in the nephrotic state (39). By the same token, vaccinations should be avoided in patients in remission, since a relapse may be precipitated.

Elimination of edema may occur "spontaneously" at times. Bed rest and restriction of sodium intake may be successful in some cases. In other instances, when renal sodium retention is marked, restriction of sodium intake only prevents further accumulation and is not followed by elimination of edema. Under these circumstances, more active measures may be taken, but the effect is usually limited, transitory, and not without some hazard.

Paracentesis or Southey's tubes promptly remove large quantities of edema fluid from patients whose edema has become heavy. If there is acute respiratory distress, pleural fluid may also be removed, but paracentesis is usually effective and somewhat safer. Since tense ascites seems to inhibit diuresis, paracentesis is often performed before other therapy is begun. A modest intake of sodium chloride (e.g., 3 Gm. per day) should be given to avoid hyponatremia after large or repeated paracentesis.

Cation exchange resins (ammonium and potassium cycle) may be given to adults in a dose of 15 Gm. after each meal to reduce the quantity of sodium absorbed. They are sometimes useful in patients who are unable to follow a low-sodium diet. Administration should be intermittent. Acidosis and disturbances of potassium balance may be encountered. Gastrointestinal irritation often limits dose and effectiveness.

Diuretics may cause a brisk increase in water and sodium elimination, with temporary relief of edema. Mercurial diuretics are most effectual. The intramuscular route is preferable to intravenous injection, which is occasionally followed by vascular collapse. Showers of red blood cells and increased proteinuria sometimes follow administration of a mercurial diuretic. Rarely, a marked decrease in renal function occurs. Aminometramide (mictine®) and acetazolamide (diamox®) are also useful. Aminophylline or osmotic diuretics (e.g., urea) are sometimes used. Sodium or potassium depletion may occur, even without striking change in urine volume or edema. Since the advent of hormone therapy, there is little need for diuretics.

Expansion of plasma volume by intravenous injection of suitable proteins or polysaccharide leads to effective removal of edema in about one half of patients with the nephrotic syndrome. Concentrated human serum albumin in a salt-poor solution, given intravenously in doses of 25 Gm. twice a day to adults, and in

somewhat smaller quantities according to surface area in children, is the most physiologic material available. When given in this dosage for four to five days, much of the administered protein is retained and utilized by the body; but if administration is continued more than four days, a large part is lost in the urine. The effects on circulating proteins and plasma volume are only temporary; but meanwhile much edema is removed, and there is subjective and objective improvement (25). Similar results are obtained after the use of dextran, gelatin, or polyvinylpyrrolidone, but febrile or anaphylactoid reactions can occur. These plasma substitutes also have the disadvantage of diluting and lowering the concentration of the natural proteins of the blood. Purified acacia produces similar effects, but prolonged depression of plasma protein formation and accumulation of the agent in the viscera have discouraged wide use.

Various chemotherapeutic agents have also been used in efforts to modify the nephrotic syndrome. Nitrogen mustard has been given intravenously for one to three days in a total dose of 0.3–0.4 mg./kg. with improvement in edema and reduction of proteinuria in a considerable proportion of the patients so treated (40). In this dosage, some nausea and vomiting usually occur, but there is little effect on the bone marrow. Thiosemicarbazone has also been administered for one month or longer, but experience with this preparation is too limited to determine its efficacy and safety. Experience has indicated that these agents have little to recommend them when compared with ACTH or cortisone therapy. Heparin has also been suggested as a possible therapeutic agent, but brief trials have produced no perceptible clinical improvement beyond some clearing of the lipemic serum.

Thyroid hormone has also been studied. Even when given in extremely large dosage, the effects have not been impressive. Evidence of hypothyroidism in nephrosis must be interpreted with special care. The low serum albumin and altered thyroxine-binding capacity of nephrotic serum may be responsible for low protein-bound iodine levels. The high serum cholesterol is not ordinarily dependent on reduction of thyroid function. Basal metabolism, also, is difficult to interpret when body weight is modified by heavy edema.

USE OF CORTICOTROPIN AND CORTICOSTEROIDS

In cases of membranous glomerulonephritis, the most important therapeutic agents in use today are pituitary corticotropin (ACTH), cortisone, and derivatives related to cortisone (14, 39, 41–49). The mode of action of these agents is not clear. If the disease is a manifestation of hypersensitivity, the 11,17-oxygenated corticosteroids may act by lowering antibody levels or by protecting the glomeruli against the damaging effect of the reaction. Alterations in levels of aldosterone and hydrocortisone (or its analogues) may alter the reaction pattern in the glomeruli. Whatever the theoretical basis, the practical result is improvement in function of the glomerular filter (14). Filtration rate is improved, and abnormal glomerular permeability is reduced. Excessive output of aldosterone is decreased (30). Diuresis usually leads to elimination of edema. Proteinuria may be unchanged, reduced, or abolished (41). In the most successful results, all detectable clinical and biochemical manifestations of disease disappear.

The earliest clinical trials seemed to indicate that ACTH was more effective than cortisone, but further observation showed that larger doses of cortisone and its derivatives gave excellent results. With increasing experience, treatment has been more aggressive; dosage has been increased and given over longer periods of time. Maximum benefit is obtained in most adult patients with the following doses: lyophilized ACTH, 25 mg. every six hours, or purified ACTH gel, 40 units every twelve hours intramuscularly; cortisone acetate, 100 mg. by mouth every six hours, or prednisone or prednisolone acetate, 20 to 25 mg. by mouth every six hours. In children, dosage may be reduced in proportion to surface area; but in resistant cases, adult doses are often well tolerated for periods of a week or two.

Steroid or corticotropin should be given in full dosage for a minimum of 10 days during the initial course of therapy. Rapoport's observations in children (42) indicate that administration of steroid for more than 18 consecutive days probably does not result in any further improvement during that course of treatment. If no improvement is evident at the end of two weeks, it has been our policy to stop therapy abruptly to take advantage of

the tendency to diuresis and reduction of proteinuria which often follows *after withdrawal* of cortisone or ACTH.

After an interval of three to seven days following the last dose of hormone, no further improvement can ordinarily be anticipated, and the situation should be evaluated. In about two thirds of all cases, edema is entirely lost. Some improvement occurs in almost all cases; but in a few, the edema is unimproved or worsened. The relief of edema, although gratifying to both physician and patient, is a temporary and symptomatic improvement. In decisions concerning further treatment, changes in urine protein are of greater importance. If proteinuria remains the same as before treatment, further intensive treatment is indicated, *provided, always, that the physician has made every effort to rule out those other diseases which give rise to a nephrotic syndrome but whose renal lesion is unresponsive to adrenal cortical hormones* (e.g., amyloidosis, disseminated lupus erythematosus, and others described under "Pathogenesis").

If remission fails to occur on the initial course, a holiday of approximately three to ten days should be allowed for maximum improvement to occur. If unusual quantities of fluid have accumulated or if other undesirable complications, such as electrolyte problems, have arisen, these should be corrected before the next course of therapy is started. A second full course of steroid or corticotropin should then be given over a period of two additional weeks in the hope of further improvement. If this fails, again after a brief interlude, a third course of therapy may be attempted.

If children do not respond well to short courses of treatment, Merrill (47) has suggested continuous administration of corticotropin (1 mg. per pound of body weight) until proteinuria decreases sharply or disappears. Daily dosage is then reduced by infinitesimal degrees over a three-month period. After this time, ACTH (1 mg. per pound of body weight) is given twice a week. The child is observed daily during this period, with special attention to middle ear, nose, throat, chest, and abdomen. Diet should contain no more than 200 mg. of sodium. Potassium salts (chloride, 3 to 5 Gm., or triplex, 6 to 12 Gm. per day) and sulfadiazine (0.5 Gm. per day) are given to all patients. Urine protein is tested regularly; protein may reappear after infection, or

if dose is reduced too quickly, or for no apparent cause. At the first return of heavy proteinuria, the dose or frequency of ACTH is doubled. If no improvement occurs in the next few days, the full program of treatment is reinstituted. These suggestions by

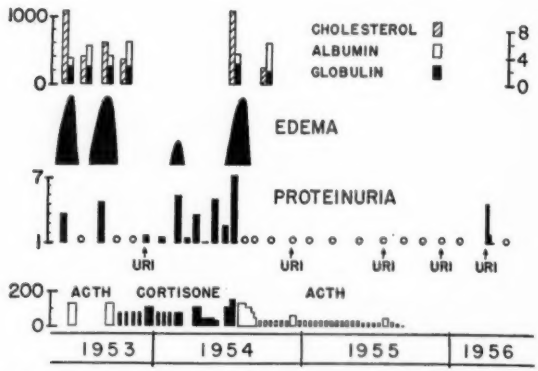

FIG. 3.—Course of a 2½-year-old male with the nephrotic syndrome illustrating intermittent, long-term hormone therapy. The nephrotic syndrome developed insidiously without obvious cause. A 10-day course of ACTH therapy produced a diuresis, disappearance of proteinuria, and return of serum protein and cholesterol toward normal. Edema and proteinuria recurred without obvious cause. Eight days of ACTH therapy again produced a diuresis and disappearance of proteinuria. While on intermittent cortisone therapy, proteinuria recurred following an upper respiratory infection. Altering dose and duration of cortisone administration did not eliminate proteinuria. In retrospect, this therapy was probably not intensive enough. Recurrence of edema and marked proteinuria responded to 1½ months of daily ACTH treatment. Intermittent ACTH administration was continued for another year. The patient remained free of edema and proteinuria despite upper respiratory infections. However, approximately 1 year after cessation of therapy, transient proteinuria developed following an upper respiratory infection. This patient was studied through the courtesy of Dr. Harold K. Faber.

Merrill deal with all ordinary contingencies in children. Side effects of prolonged corticotropin administration occur regularly but have not been serious if the child is seen daily. Complications make this treatment too risky for adults or for the child who

cannot be so closely followed. Figure 3 illustrates successful use of continuous ACTH therapy in a patient who showed increasing resistance to previous treatment.

Of those patients who show great improvement in fluid balance and proteinuria after one or more short courses of treatment, a substantial number require some form of maintenance therapy. The frequency of relapse following discontinuance of therapy is highest in the first few months. After a year's freedom from signs of disease, recurrence is infrequent. Maintenance therapy must be continued at a high dosage, either according to the plan of intermittent heavy dosage suggested by Lange or the continuous administration as devised by Merrill.

Intermittent maintenance therapy has the advantage of causing a less striking degree of hyperadrenocorticism than that observed after continuous administration of corticotropin. Lange (48) has suggested that cortisone (100 mg. every six hours) be given for three consecutive days of each week for 12 to 30 weeks. Sustained improvement in a boy receiving cortisone 100 mg. three times a week is shown in Figure 4. Smaller doses and shorter duration of treatment are not always so successful in avoiding relapse. In the case illustrated in Figure 3, recurrence of proteinuria followed upper respiratory infection while the child was receiving cortisone 75 mg. three days each week. Relapse may be precipitated by respiratory infection or may occur spontaneously; in this event, full treatment daily for two weeks is advised.

The question frequently arises whether to embark immediately on long-term treatment after a good result follows the initial heavy course of steroid. It appears that those patients who respond most promptly and completely to the initial course of therapy have a better chance of going on without recurrence of their disease than those patients whose response is sluggish and incomplete. It is also easy to remember patients who responded brilliantly at first but who subsequently relapsed and failed to respond to subsequent administration of steroids. In spite of the hazards of long-term, high-dose steroid therapy, patients treated according to a scheduled plan over longer periods remained in better condition. Furthermore, relapses were fewer; resistance to steroid treatment did not develop; and there was increased survival rate as compared with patients who received short

courses of treatment only (49). Most experienced observers favor some form of therapy beyond the initial course, even if full remission occurs on that occasion. The duration of such therapy may be measured against the probability of relapse. The following factors may be helpful: the individual's past history,

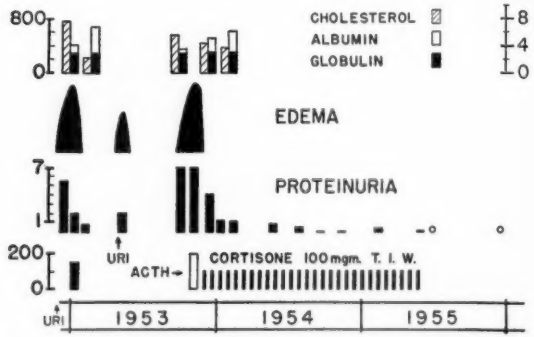

FIG. 4.—Course of a 9-year-old male with the nephrotic syndrome illustrating intermittent, long-term therapy. The nephrotic syndrome followed upper respiratory infection. A 2-week course of cortisone therapy produced a diuresis with loss of edema, decreased proteinuria, and return of serum protein and cholesterol toward normal. Proteinuria did not disappear. Following another upper respiratory infection, there was an increase in proteinuria and transient accumulation of edema. Recurrence of marked proteinuria and edema responded to 15 days of ACTH therapy. Proteinuria, however, did not disappear until after 1½ years of intermittent administration of cortisone. The patient continues to be well without proteinuria. This patient was studied through the courtesy of Dr. Harold K. Faber.

response to treatment, season of the year, susceptibility and exposure to respiratory infection, and other environmental hazards.

Adults appear to respond to treatment about as well as children. Of all our patients who received comparable short-term treatment with corticotropin or cortisone, 44% of children and 43% of adults were well and showed normal urine tests one to three years after the last treatment (41). Results of long-term therapy have also been similar in adults and children (50, 51).

Whenever large doses of corticotropin or corticosteroid are

given for more than a few days, the patient should be under close observation. Weight and blood pressure are recorded each day. Full doses of an effective broad-spectrum antibiotic should be administered throughout such intensive courses of therapy. The patient should be kept at bed rest or on limited activity, taking into account the edema, respiratory difficulty, hypertension, and other individual factors. Aluminum hydroxide gel usually controls epigastric burning or pain. Hemorrhage or perforation of peptic ulcer might be encountered. Sodium intake should be limited, but not too strictly. A diet containing 3 Gm. of sodium chloride per day is suitable for most patients. Potassium salts should not be administered during the first few days of corticosteroid therapy, when oliguria is common, but potassium chloride (3 to 5 Gm. per day) or other potassium salts are indicated as soon as diuresis increases. Larger doses may be necessary if there is profuse diuresis during the course of therapy. Serum sodium and potassium determinations should be made before starting treatment, after two days of treatment, and at intervals thereafter as fluid balance changes. Lassitude, failure of appetite, rise in blood pressure, or marked changes in weight or fluid balance call for prompt study of serum electrolytes. If the blood pressure rises above 150/100 in adults, or somewhat lower levels in children, or if there is a sharp rise in blood pressure, the situation should be evaluated at least once each day, and treatment should be reduced or stopped promptly if blood pressure continues to increase. Headache may be the first symptom of encephalopathy; nausea, stupor, convulsions, and lasting cerebral damage can ensue if warnings of hypertension, headache, oliguria, and hyponatremia are not heeded.

Almost all patients show reduced urine volume, gain in weight, and increased proteinuria during the first week of corticosteroid administration. Toward the end of the first week or during the second week, the situation usually takes a more favorable turn. Diuresis increases, and proteinuria usually shows some decline. If signs of improvement have not occurred at the end of two weeks of treatment, therapy may be discontinued abruptly; the ensuing diuresis is sometimes so profuse that the patient may require some circulatory support in the form of infusion of saline solution, albumin, or blood.

Disturbances of electrolyte balance are common in the nephrotic syndrome (52). Long-continued low-sodium diet, diuretics, and removal of effusions by tapping may lead to hyponatremia. This should be remedied before steroid therapy is undertaken, since hyponatremia and hyperkalemia may be aggravated when ACTH or steroids are first administered. Potassium depletion and dehydration may appear following profuse diuresis. Such changes can often be anticipated by following fluid intake, urine volume, and body weight before serious distortion of extracellular electrolytes becomes apparent. If there is an actual deficiency of electrolyte (e.g., dehydration or potassium depletion), replacement of the deficiency is indicated. If, however, the problem is related to oliguria (e.g., hyponatremia plus edema, or high serum potassium), intravenous albumin often improves renal function and corrects the problem at its source.

Infection may occur in spite of prophylactic antibiotic therapy. Symptoms and signs of infection may be "masked" by corticosteroid excess. There may be no localizing complaint, and fever may be reduced or absent. The only signs at onset may be unusual lassitude, irritability, and failure to eat. Leukocytosis is difficult to evaluate, since it occurs regularly without infection during corticosteroid administration. A likely local site of infection is usually revealed by careful physical examination. Peritonitis is especially frequent in children, and blood culture is advisable in all cases. Local cultures should be taken immediately in order to determine the sensitivity of invading organisms. If the infection is not promptly controlled, dosage of corticosteroid should be reduced.

Thrombosis and thromboembolic manifestations may occur at any time in the nephrotic syndrome. There is no definite evidence that thrombosis is more frequent during administration of corticosteroids. Some observers feel that rapid reduction in dosage may increase the risk. Conservative management is usually adequate. Anticoagulant therapy may be used.

Significant slowing of growth is likely to occur in children who receive more than 45 mg. of cortisone per square meter for more than a few weeks (53). Even if steroid therapy is not given, children with nephrosis show temporary impairment of growth. In either case, the retardation of growth is quickly made up when the

disease process stops or when steroid therapy is reduced below the critical level.

The low serum calcium level in the nephrotic syndrome is usually attributed to reduction of serum proteins. Tingling and muscle cramps occurring during corticosteroid administration may be relieved by administration of calcium gluconate.

Glycosuria is frequently observed in patients receiving high doses of corticotropin or corticosteroids. The blood sugar is seldom increased far above normal. If heavy glycosuria or hyperglycemia above 200 mg./100 ml. is noted, dosage of corticosteroid should be reduced. Diabetic acidosis or permanent diabetes are rare complications.

These problems can usually be controlled by close attention and by anticipation or prompt therapy. It is noteworthy that those groups who are most closely in touch with the results of steroid therapy are becoming increasingly aggressive in its use as the years go by. There is a feeling that undue conservatism has resulted in inadequate treatment and failure to control the progression of the renal lesion in certain instances. The hazards of long-term steroid therapy, under scrupulous control, are not as serious as the long-term outcome of the nephrotic syndrome.

Even after the patient seems entirely well, urine should be tested at regular intervals with sulfosalicylic acid. When proteinuria appears, frequently after respiratory infection, it may prove so transitory that treatment is not needed. In other instances, heavy and continued proteinuria ushers in a full-blown relapse. Fortunately, such recurrences seem to be less and less frequent after a year or more in remission.

MANAGEMENT OF HYPERTENSION AND UREMIA

In chronic forms of the nephrotic syndrome, *hypertension* frequently appears as renal function fails. In some instances, hypertension may be temporary, due to a flare-up of the renal lesion or an untoward reaction to corticosteroids. In the majority of cases, however, hypertension begins insidiously and increases steadily as renal insufficiency develops. In the presence of frank renal failure, efforts to reduce the blood pressure usually do more harm than good.

A few patients develop marked hypertension before renal insufficiency is evident. If headache, visual disturbance, retinopathy, or cardiac failure are present, treatment with hypotensive agents is justified. The presence of a renal lesion without appreciable renal insufficiency is not a contraindication to the use of hypotensive agents. Marked symptomatic and objective improvement has followed reduction of greatly increased arterial pressure in patients of this type. The prognosis is obviously grave, but a year or more of useful life may be possible.

The management of the *azotemic and terminal stages* of the nephrotic syndrome is conservative and symptomatic. A simple diet, high in carbohydrate and low in protein, is offered. Water and sodium intake are as free as can be tolerated without undue accumulation of edema. Nausea and vomiting interfere with adequate nutrition and oral medication. If dehydration and ketosis appear, intravenous feeding for a day or so may make the patient feel much better. Anemia accentuates weakness and dyspnea to some extent, but blood transfusion is seldom necessary unless hemoglobin concentration falls to approximately 7 Gm./100 ml. Infusion of fresh packed red blood cells increases hemoglobin level with less expansion of blood volume than that seen after whole blood transfusion. Careful matching and slow administration of blood are important, since heart failure or suppression of urine may ensue. Morphine or paraldehyde may be used to allay discomfort or restlessness.

The nephrotic syndrome still presents many problems and challenges to the physician and investigator. The clinical picture is so typical as to leave little doubt in the average case, but vital questions concerning the underlying disease are unanswered. How did it arise and what will be the outcome? How can we tell the benign case from one which is to go on to renal insufficiency? What factors determine or affect the course? Does treatment really alter the long-term outcome? We can answer these questions only in part or in statistical form. The answers provide limited satisfaction to the physician, the patient, and his family. Active clinical investigation promises more efficient use of known agents, but much fundamental information is still to be discovered.

Meanwhile, the physician can use present knowledge to advantage. One has only to look back a few years to the era before antibiotics and corticosteroids to remember a long, debilitating illness, full of discomfort, punctuated by repeated crises. Much of the day-to-day misery is unnecessary now, thanks to newer agents. But the new agents have brought with them new responsibilities: more watchfulness, more physiologic understanding, more laboratory support. The immediate financial burden of the disease is increased by intensive study and treatment, but in the long run it is worth while if a worker is rehabilitated or a child is spared a long period of illness.

The role of the family physician is a difficult but important one. The medical, personal, and economic burdens are heavy. If the disease drags on, if treatment is not completely successful, if prognosis is uncertain, the strain on the patient-physician relationship is increased. Patients tend to gravitate to university hospitals or other centers where special advice and laboratories are available and where advances are in the making through detailed study and follow-up of larger groups of patients. The consultant or medical center distant from the patient's home does not replace the family physician, but such supplementary services should be called on early if they are to be used effectively. In co-operation with these facilities, the personal physician provides the essential strong point of confidence and continuity of care at home.

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